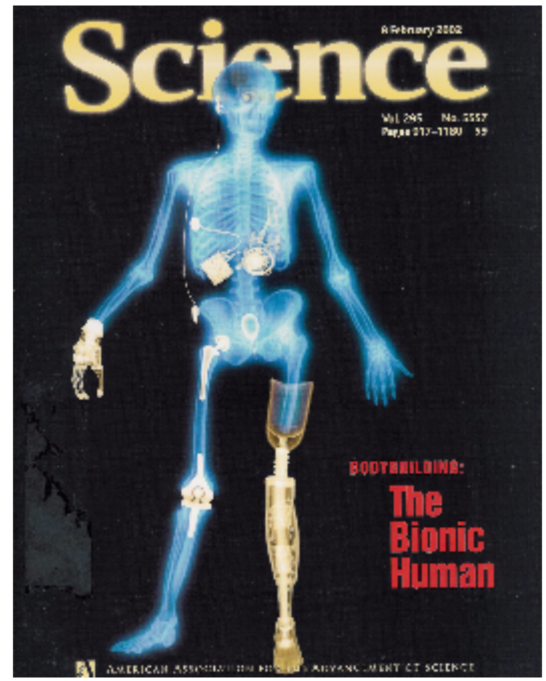
Demystifying medicine: transplantation and replacement therapy for heart failure

Jonah Odim

April 22,2014

NIAID



Pediatric Organ Transplantation* 2005

Organ	Transplants	Total transplants (%)
Kidney	890	16,477 (5.4)
Liver	569	6,443 (8.8)
Lung	54	1,406 (3.8)
Intestine	96	178 (54)
Pancreas	26	541 (4.8)
Heart	313	2,125 (14.7)
K/P	7	903 (0.8)
Heart/Lung	5	35 (14.3)
Total	1,960	28,108 (7%)

***Children awaiting transplantation = 2,187/99,383 (2.2%)**

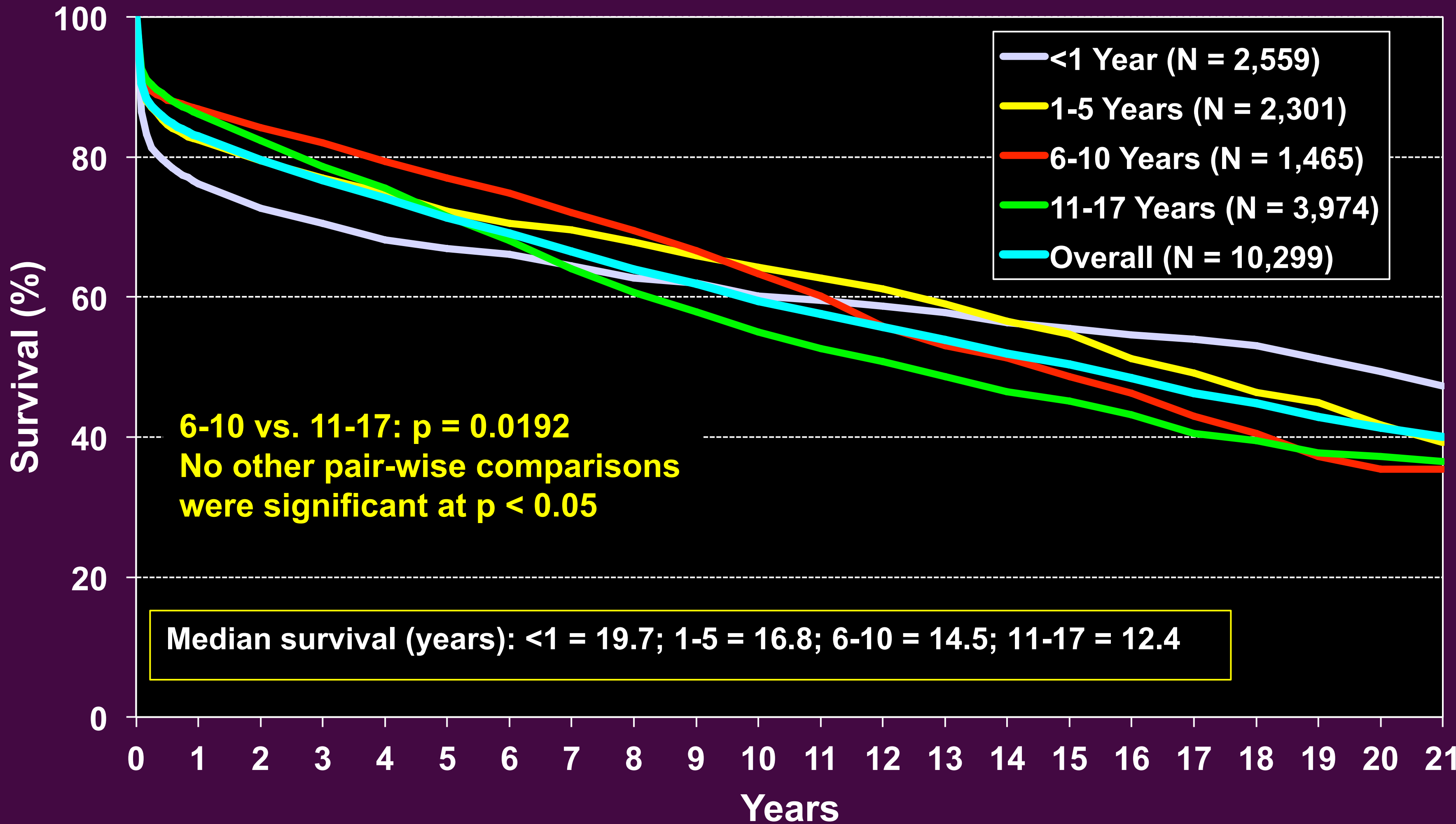
Organ	1-year graft survival (%)	1-year patient survival (%)
Kidney	92	96
Liver	82	86
Heart	87	87
Kidney + Pancreas	91	95
Pancreas	78	95
Lungs	82	84
Small Intestine	78	84
	~85%	~90%

Solid Organ Transplantation
Long-term failure

	Graft Survival (%)			
	1-year	3-year	5-year	10-year
Kidney	92	82	68	38
Heart	87	79	68	48
Lung(s)	82	58	49	-

NATCO The Organization for Transplant Professionals

Pediatric Heart Transplants
Kaplan-Meier Survival (Transplants: January 1982 – June 2011)



Persisting Pestering Problems

1) Supply/demand imbalance

2) Morbidity from immunosuppression (e.g., renal, cardiovascular, infectious, malignancy)

3) Chronic rejection/injury and graft loss

4) Competing and emerging therapeutics (e.g., mechanical circulatory assistance, xenotransplantation, stem cells, whole organ engineering)

Key knowledge gaps

1) How can we optimize and individualize therapies and improve late graft outcomes mediated by immune and non-immune factors

2) Expansion and optimization of the donor and recipient pool

3) Optimize and individualize IS therapies and improve late allograft outcomes mediated by immune and non-immune factors

4) Characterize and understand antibody mediated rejection

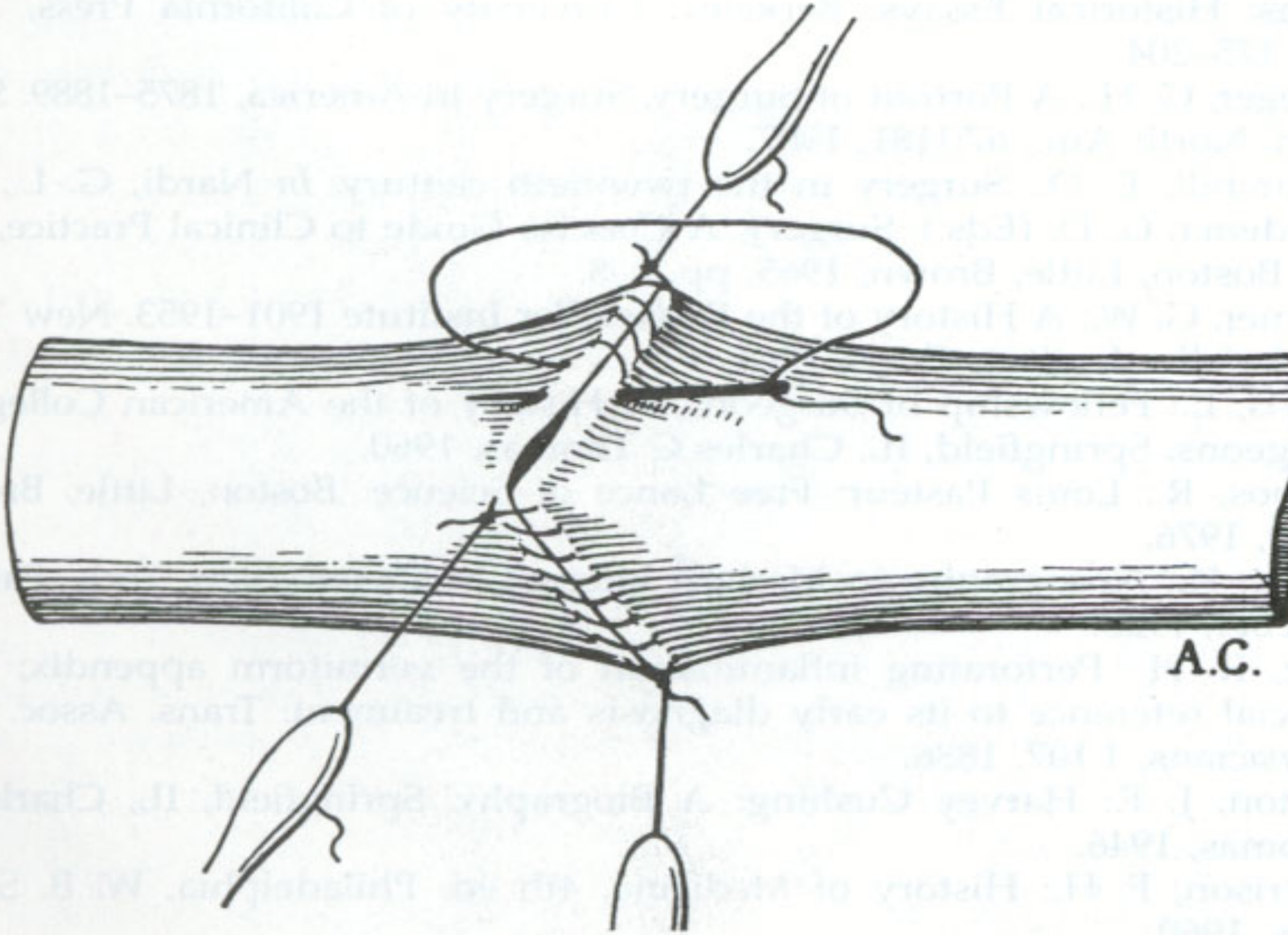


Figure 1–20. Joining blood vessels by suture anastomosis. This representation is adapted from the line drawing by Alexis Carrel published in *Lyon Medical* in 1902. The walls of the two blood vessels (here drawn as about 5 mm. in diameter) are held together by three holding sutures. Another is then used to sew over and over, with very fine needles ("aiguilles extrêmement fines"). This method of suture anastomosis, demonstrated initially by Carrel, is still used throughout surgery, and particularly in the transplantation of organs.

ANNALS OF SURGERY

VOL. 132 NOVEMBER, 1950 No. 5

HYPOTHERMIA

ITS POSSIBLE ROLE IN CARDIAC SURGERY:

AN INVESTIGATION OF FACTORS GOVERNING SURVIVAL IN DOGS AT LOW BODY TEMPERATURES*

W. G. Bigelow, M.D., W. K. Lindsay, M.D.,
and W. F. Greenwood, M.D.

Toronto, Canada

From the Departments of Surgery, Pathological Chemistry and Medicine of the University of Toronto

The use of hypothermia as a form of anesthetic could conceivably extend the scope of surgery in many new directions. A state in which the body temperature is lowered and the oxygen requirements of tissues are reduced to a small fraction of normal would allow exclusion of organs from the circulation for prolonged periods. Such a technic might permit surgeons to operate upon the "bloodless heart" without recourse to extra corporal pumps, and perhaps allow transplantation of organs.

At the present time, pericardectomy as well as operations designed to revascularize[1, 2, 3] or repair[4] the myocardium are in the process of development; these involve the heart wall. Most so-called heart operations, however, are restricted to the anastomosis of vessels about the heart, the most notable in this category being the current operations for congenital heart disease[5, 6] and a shunt[7] for mitral stenosis. Intracardiac procedures upon human beings are heroic technics designed to open a stenosed mitral valve and close[11] or produce[12] a septal defect in an intact heart with little or no visual control. All these procedures represent advances in our knowledge, but the human heart until now has resisted serious inroads by the surgeon. The shunt operations produce a secondary, although less serious, defect and intracardiac operations under direct vision are still not possible.

A bloodless heart excluded from the circulation is necessary before much further progress can be made in the field of cardiac surgery. Methods to short circuit the heart by an extra corporal heart-lung pump have been under experimental study in different centers[13-16] for several years. We have used

* Financed in part by a Defence Board of Canada grant. Submitted for publication November, 1949.

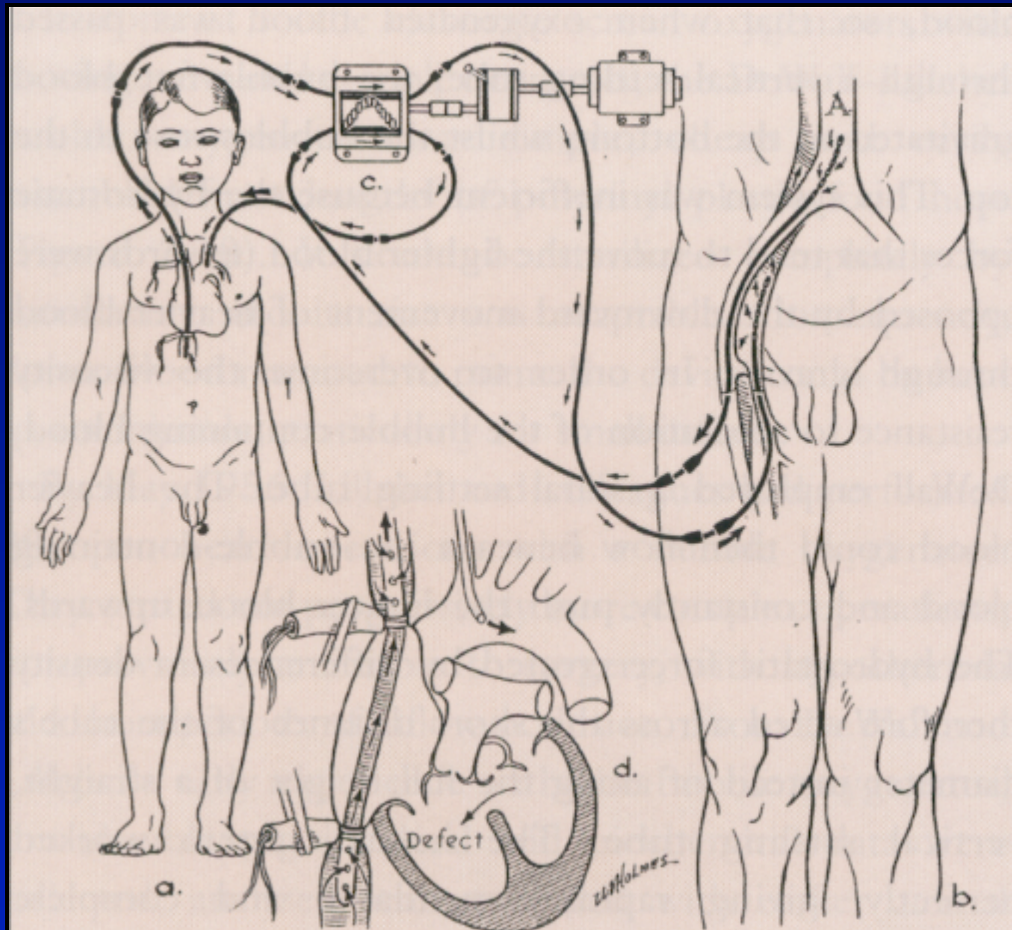
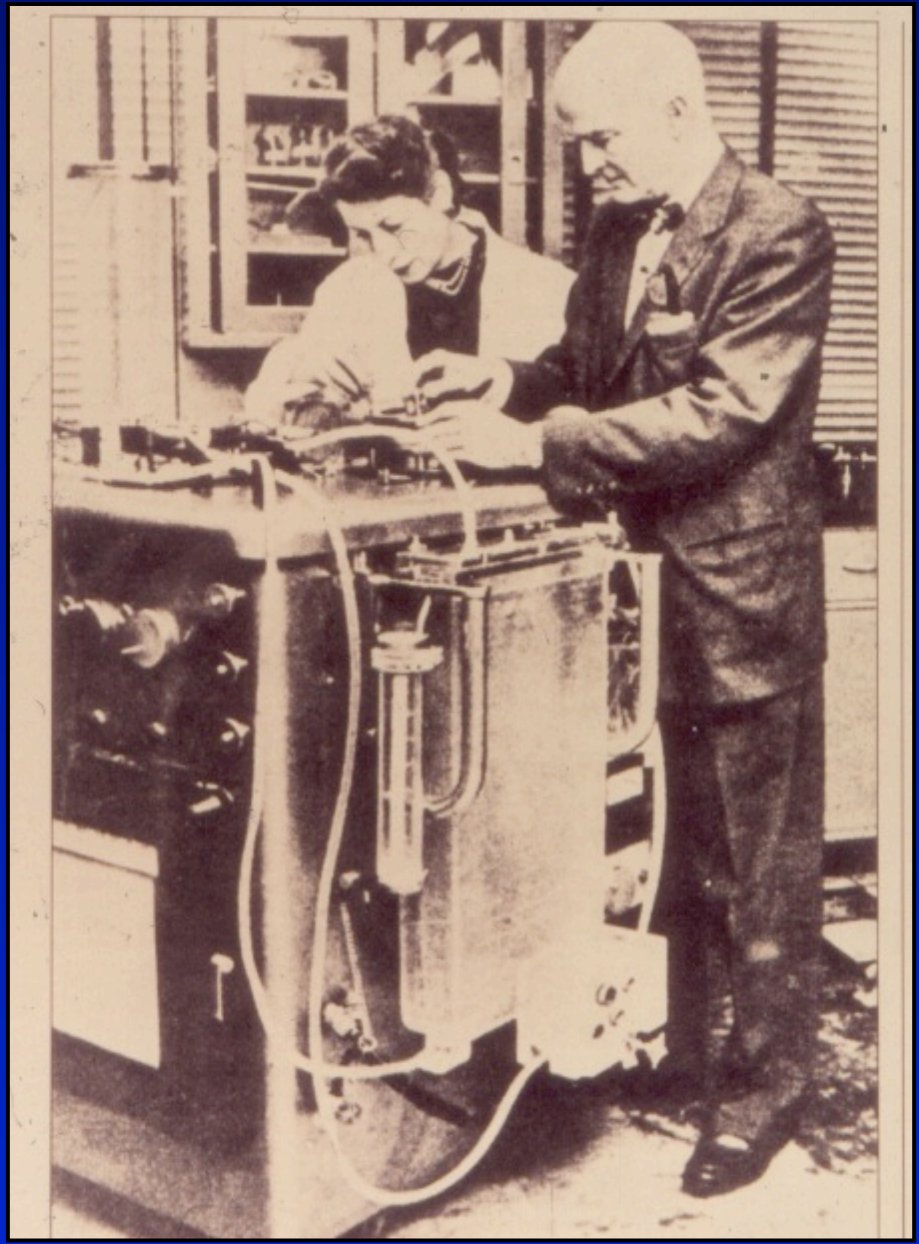


FIG. 1. Method of linking donor and patient for direct vision intracardiac surgery. a, Patient: showing sites of arterial and venous cannulations. b, Donor: showing sites of arterial (superficial femoral) and venous (saphena magna) cannulations. c, The pump assembly: Consisting of an electric motor, a speed changer, and the pumping unit. The pump consists of multiple cam operated metal fingers that massage the blood contained within the tubing. d, A magnified view of the patient's heart showing the plastic vena caval catheter which has been inserted through the internal jugular vein in the neck and positioned so that venous blood is withdrawn from both cavae during the interval of total cardiac by-pass. Note also the relative positions of the vena caval occluding tapes for securing inflow stasis during the intracardiac procedure. The arterial blood from the donor is circulated to the patient's body via the catheter inserted into either the right or left subclavian artery.

Lillehei's Cross-Circulation Diagram

Dad = heart-lung machine
Son = subject with hole in heart

CROSS-CIRCULATION IN THE OPERATING ROOM



John Heysham Gibbon and his wife

The Cape Argus Newspaper after the First Human Heart Transplant

wedding garters ...

Stuttafords

The Cape Argus

CITY LATE

WONDOSOL

Patient's condition 'first class', Groote Schuur doctors say

CRISIS AFTER 7 DAYS

MAN WITH A NEW HEART

Three years' work on 'op'

Louw tells of key factor in heart transplant

Crucial time

They will miss Denise...

And a surgeon took the pictures, too!

Woman had no chance of survival

Her kidney helps a boy (10)

DAVIS CUP: SPAIN WINS. REPORT Page 2

Other pages

Partly cloudy

This month 5 people have died on W.P. roads

HEAD OF TEAM

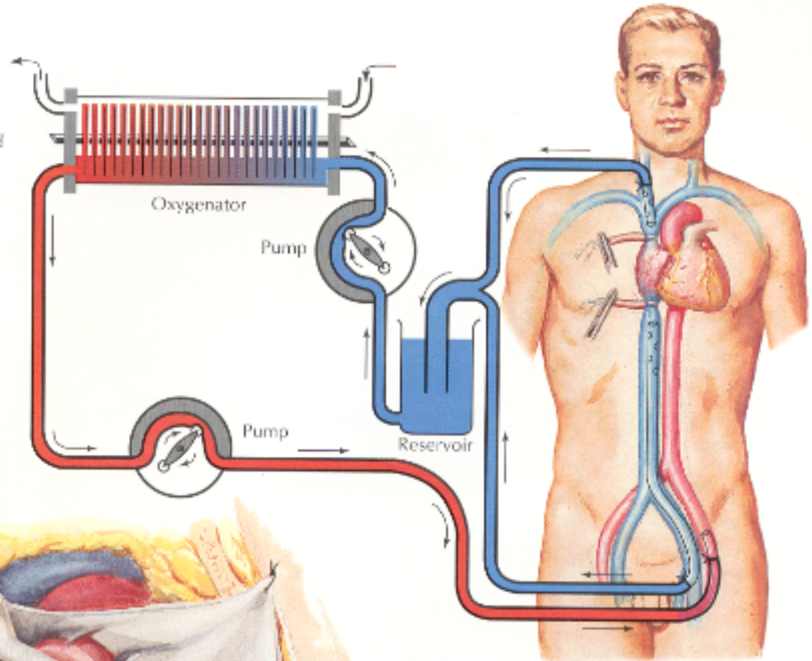
CHURCHMEN APPROVE

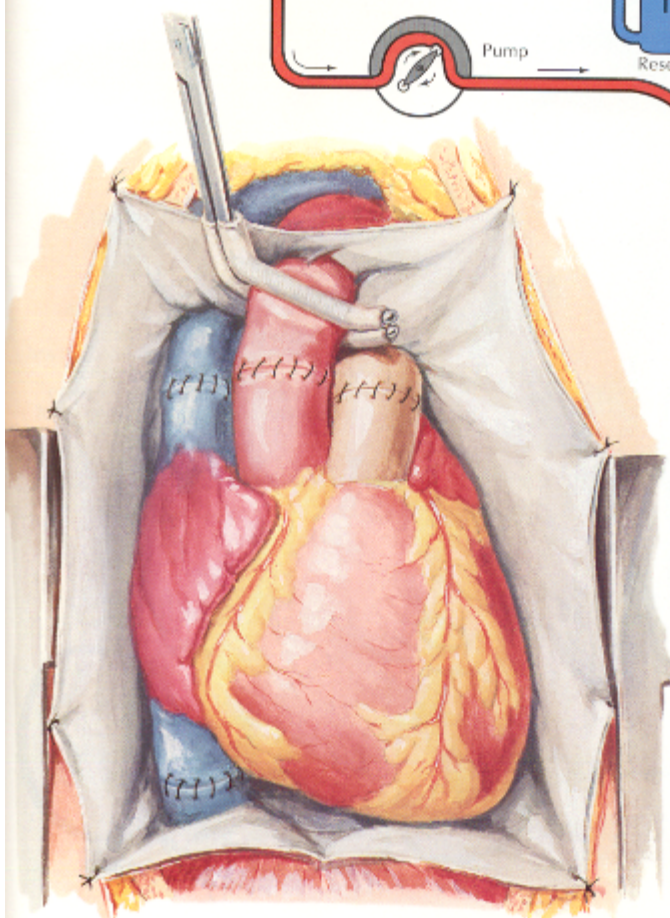
LOOK MA! NO PINS...

Snap Nappy

Christiaan N. Barnard

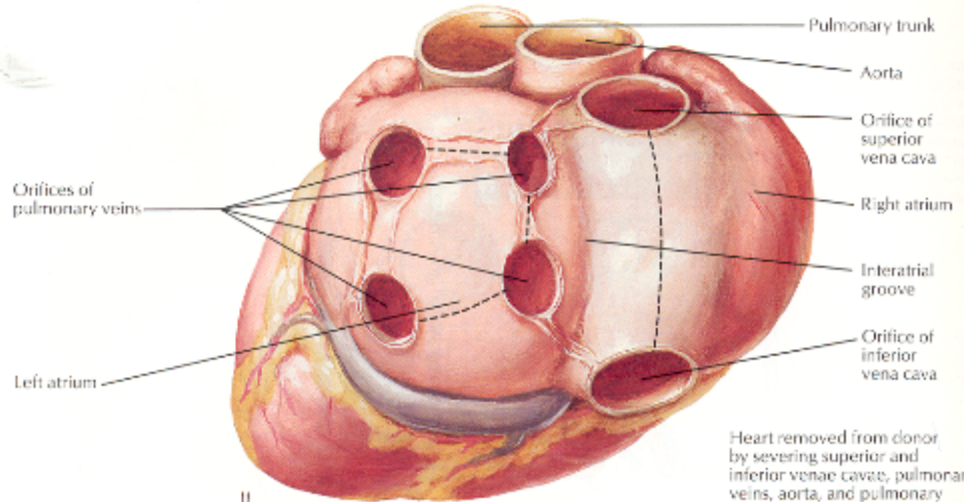
Diagram of extracorporeal circulation; superior and inferior venae cavae cannulated by catheters introduced, respectively, via internal jugular vein and saphenofemoral junction, thus leaving operative field free



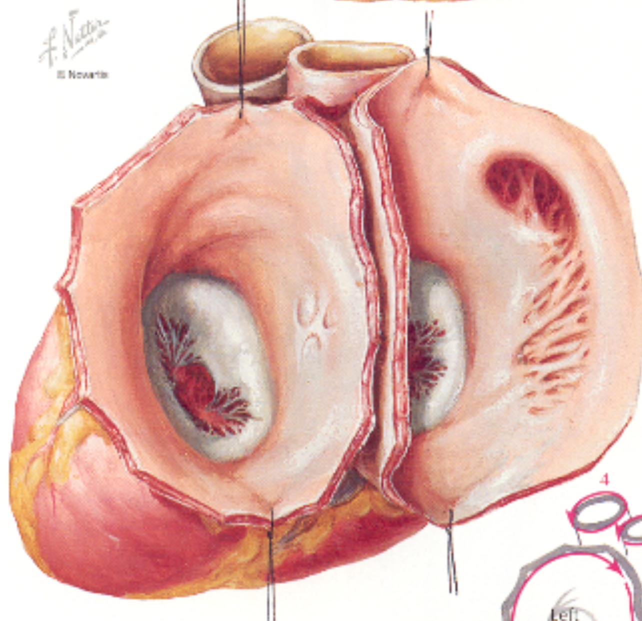


Recipient's thorax opened by midline sternum-splitting incision; pericardium incised longitudinally and stitched to wound edges; tapes passed around venae cavae and tightened as patient is placed on extra-corporeal circulation; aorta clamped. (Broken lines indicate levels for transection of aorta and pulmonary trunk)

Heart Transplantation: Donor Heart



Heart removed from donor by severing superior and inferior venae cavae, pulmonary veins, aorta, and pulmonary trunk (viewed from rear). (Broken lines indicate incisions to connect caval orifices and vein orifices, thus opening the atria without dividing the septum)



The flaps created by the incisions indicated above have been turned out and drawn longitudinally by sutures, thus extending the septum and atrial walls to accommodate to larger heart of recipient

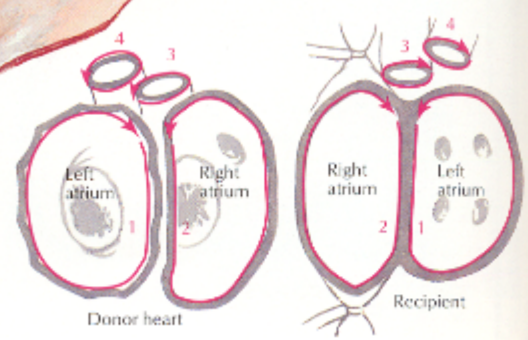
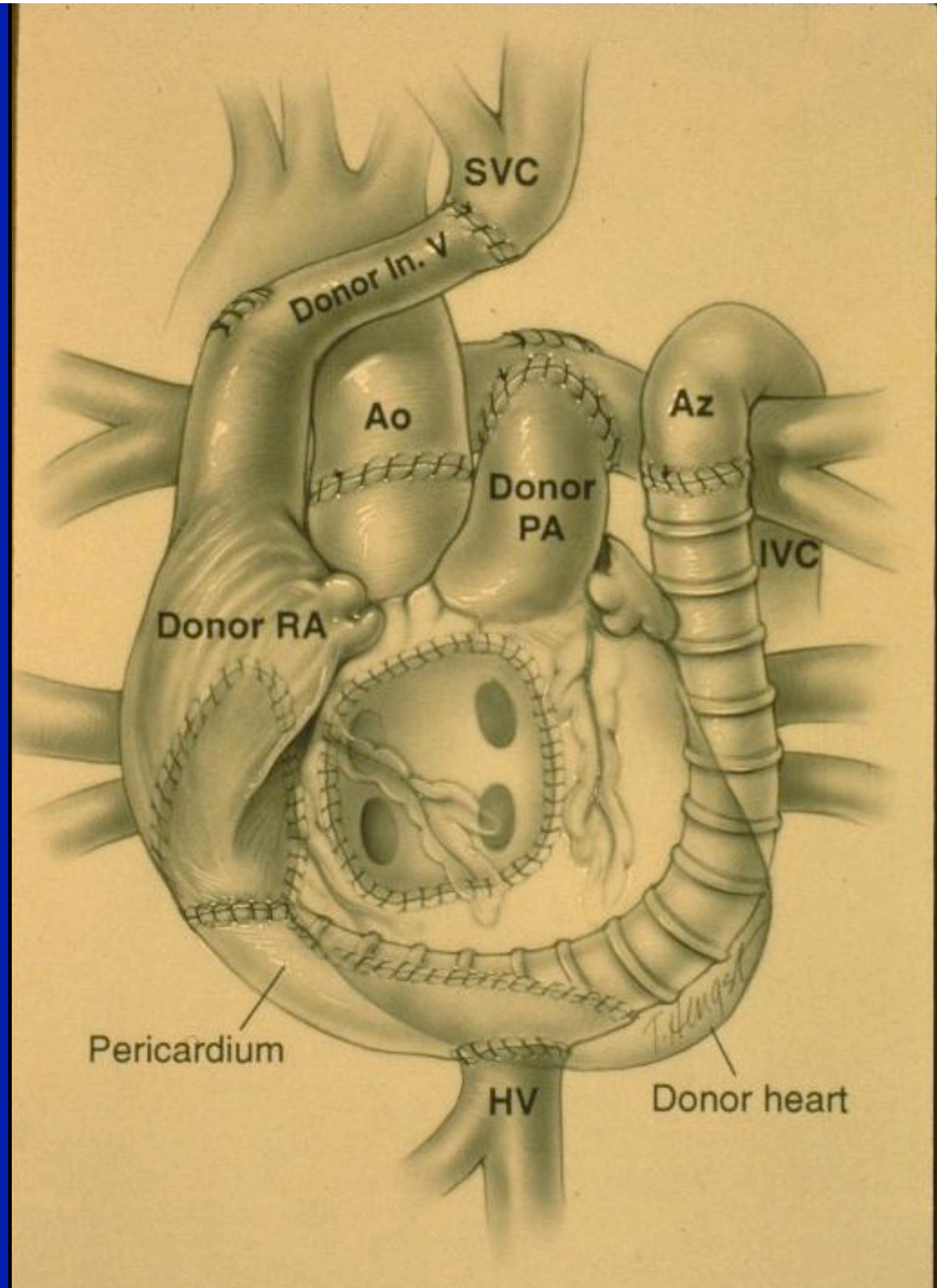
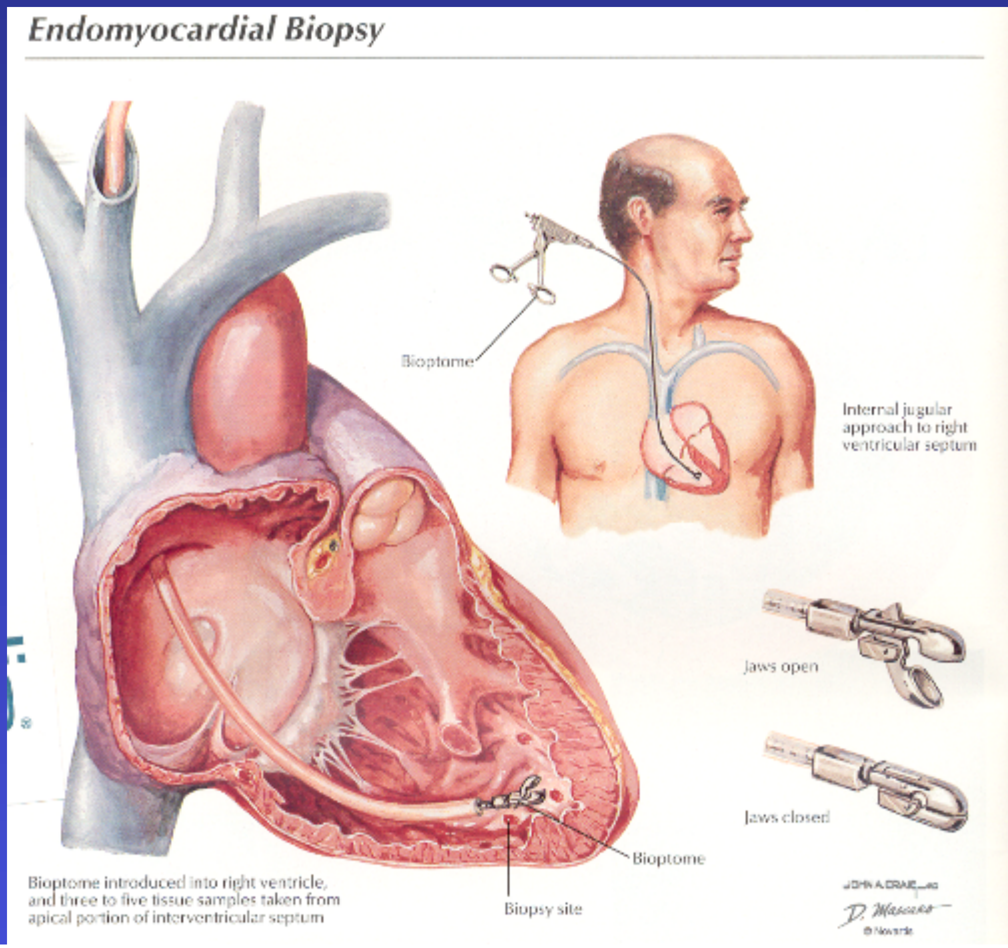


Diagram to indicate successive continuous sutures to be employed in uniting donor heart to recipient


SVC
Donor In. V
Ao
Az
Donor
PA
IVC
Donor RA
Pericardium
HV
Donor heart

Diagnosis of human cardiac allograft rejection by serial cardiac biopsy

Philip K. Caves, F.R.C.S., Edward B. Stinson, M.D., Margaret E. Billingham, M.D., Alan K. Rider, M.D., and Norman E. Shumway, M.D., Stanford, Calif.



Pathology of Transplantation

- **Effects of immunosuppression**
  - **drug toxicity**
  - **infection**
  - **neoplasia**
- **Allograft rejection**
  - **humoral (antibody-mediated)**
  - **cellular**
  - **chronic injury**

Therapy categories

Induction = therapy at start of transplant; typically consists of methylprednisolone and/or antibody preparations (lymphocyte depletion)

Maintenance = chronic therapy

Desensitization = therapies to reduce newly formed or pre-existing alloantibodies; IV Ig or Cyclophsophamide, Rituximab (anti-CD 20 antibody), Bortezomib, Eculizumab

Basic Immunosuppression

Maintenance	Induction
Steroids	Basiliximab
Azathioprine	Daclizumab
Mycophenolate mofetil (MMF)	OKT3
Cyclosporine	ATGAM
Tacrolimus	Thymoglobulin
Sirolimus	
Belatacept (FDA approved-2011)	Alemtuzumab (Campath-1H)

Side Effects of Chronic Immunosuppression

Infectious
- Viral
- Fungal
- Bacterial

Malignant
- Lymphoma
- Skin

Toxic
- Renal
- Cardiovascular (hypertension, hyperlipidemia)

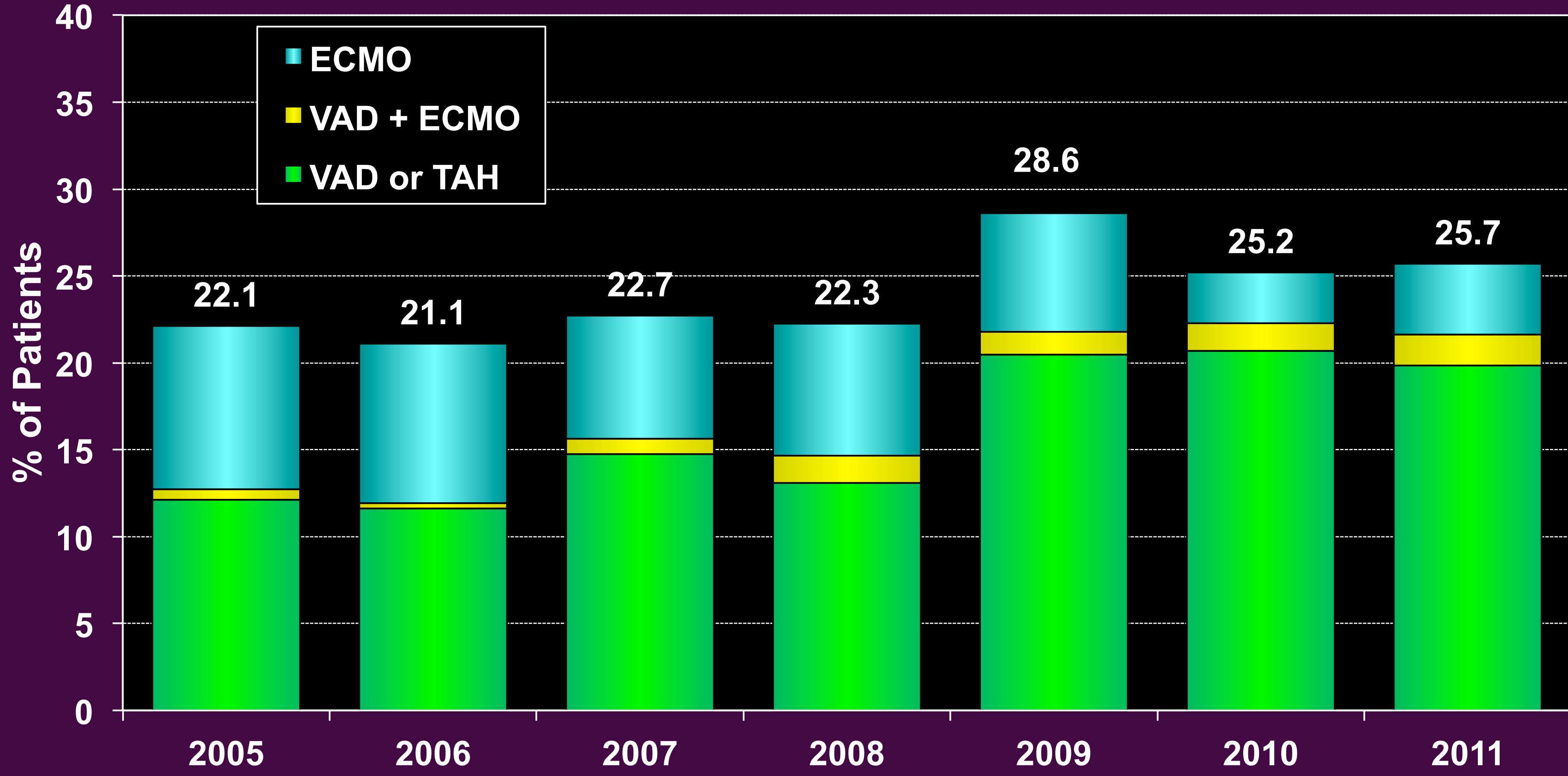
Metabolic
- Diabetes
- Osteoporosis

Cosmetic
- Hirsutism
- Acne

Immunotherapy is a Balance

- Immunosuppression prevents rejection and is required indefinitely post-Tx
- Immunosuppression has risks: infection, malignancy, toxicity
- Finding the balance is an important task but there is no established objective measure of immunosuppression

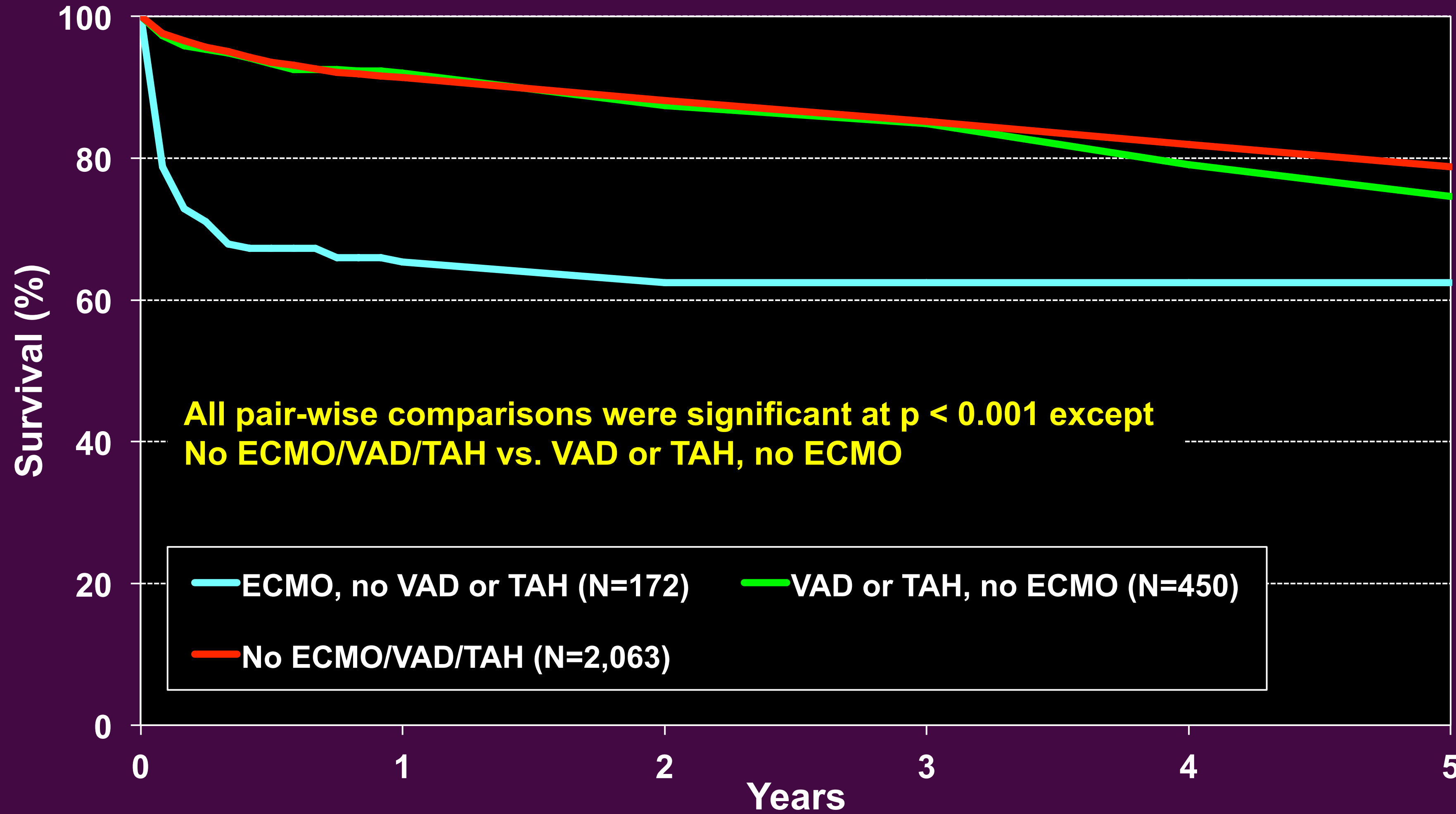
Pediatric Heart Transplants
% of Patients Bridged with Mechanical Circulatory Support* by Year (Transplants: January 2005 – December 2011)



* LVAD, RVAD, TAH, ECMO

ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
2013
JHLT. 2013 Oct; 32(10): 979-988

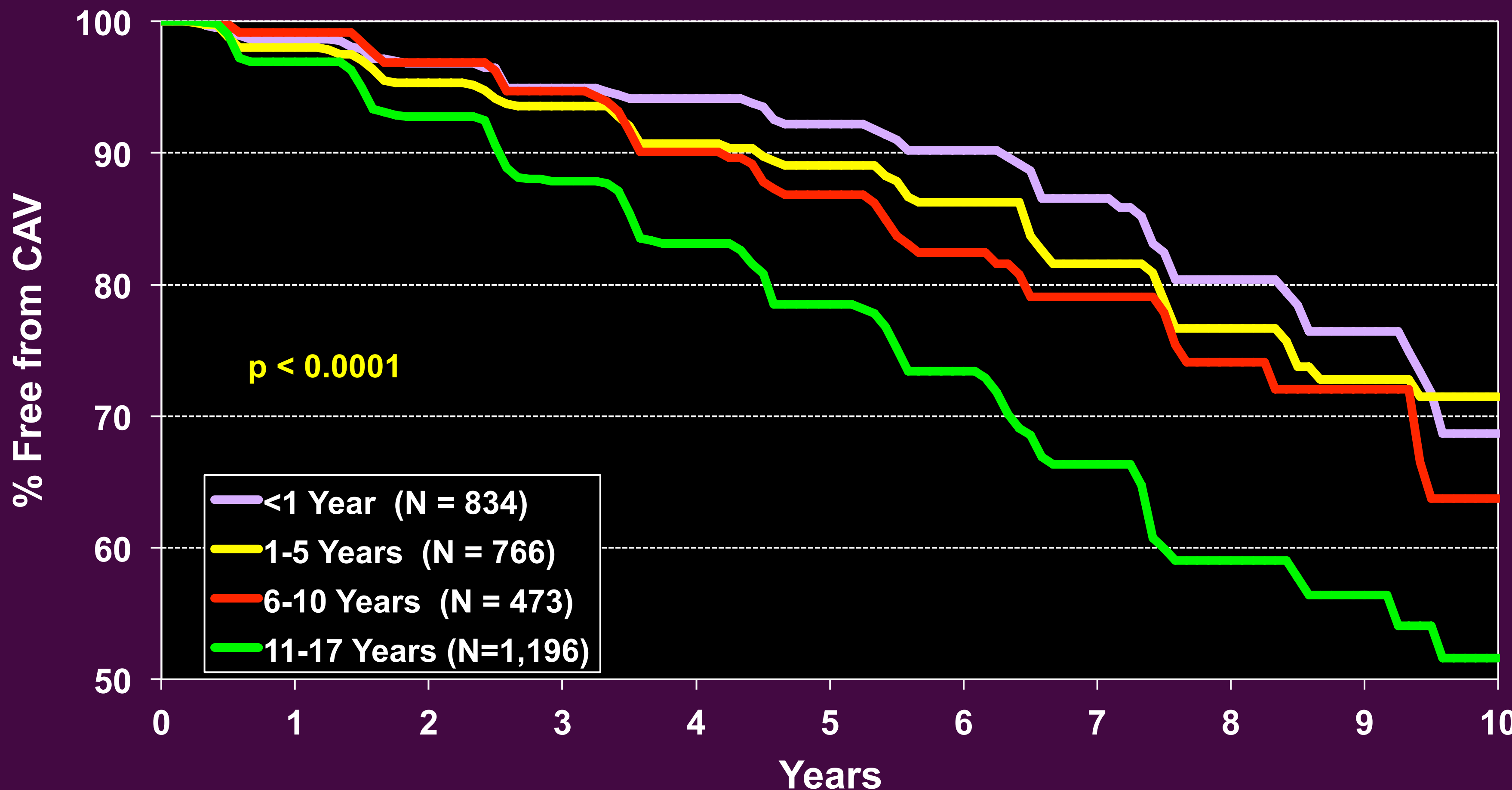
Pediatric Heart Transplants
Kaplan-Meier Survival by Mechanical Circulatory Support Usage* (Transplants: January 2000 – June 2011)



* LVAD, RVAD, TAH, ECMO

2013
ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
JHLT. 2013 Oct; 32(10): 979-988

Pediatric Heart Transplants
Freedom from Coronary Artery Vasculopathy by Age Group (Follow-ups: 2000 – June 2012)



PEDIATRIC HEART TRANSPLANTS (2001-2010)
Risk Factors For 1 Year Mortality

VARIABLE	N	Hazard Ratio	P-value	95% Confidence Interval
ECMO	280	2.65	<.0001	2.00-3.50
Retransplant	206	2.16	0.0003	1.42-3.27
Congenital diagnosis	1426	2.04	<.0001	1.58-2.64
On dialysis	123	2.03	<.0001	1.42-2.90
Donor cause of death = cerebrovascular/stroke vs. head trauma	327	1.53	0.009	1.11-2.11
Donor cause of death other than (head trauma, cerebrovascular/stroke, anoxia and CNS tumor) vs. head trauma	289	1.49	0.027	1.05-2.12
Male donor/female recip vs. male donor/male recip	913	1.44	0.006	1.11-1.88
Prior sternotomy	830	1.42	0.007	1.10-1.83
On ventilator	700	1.35	0.017	1.06-1.73
PRA > 10%	311	1.35	0.05	1.00-1.81
Infection requiring IV drug therapy (within 2wk/TX)	610	1.32	0.027	1.03-1.69
Donor cause of death = anoxia vs. head trauma	902	0.75	0.026	0.58-0.97

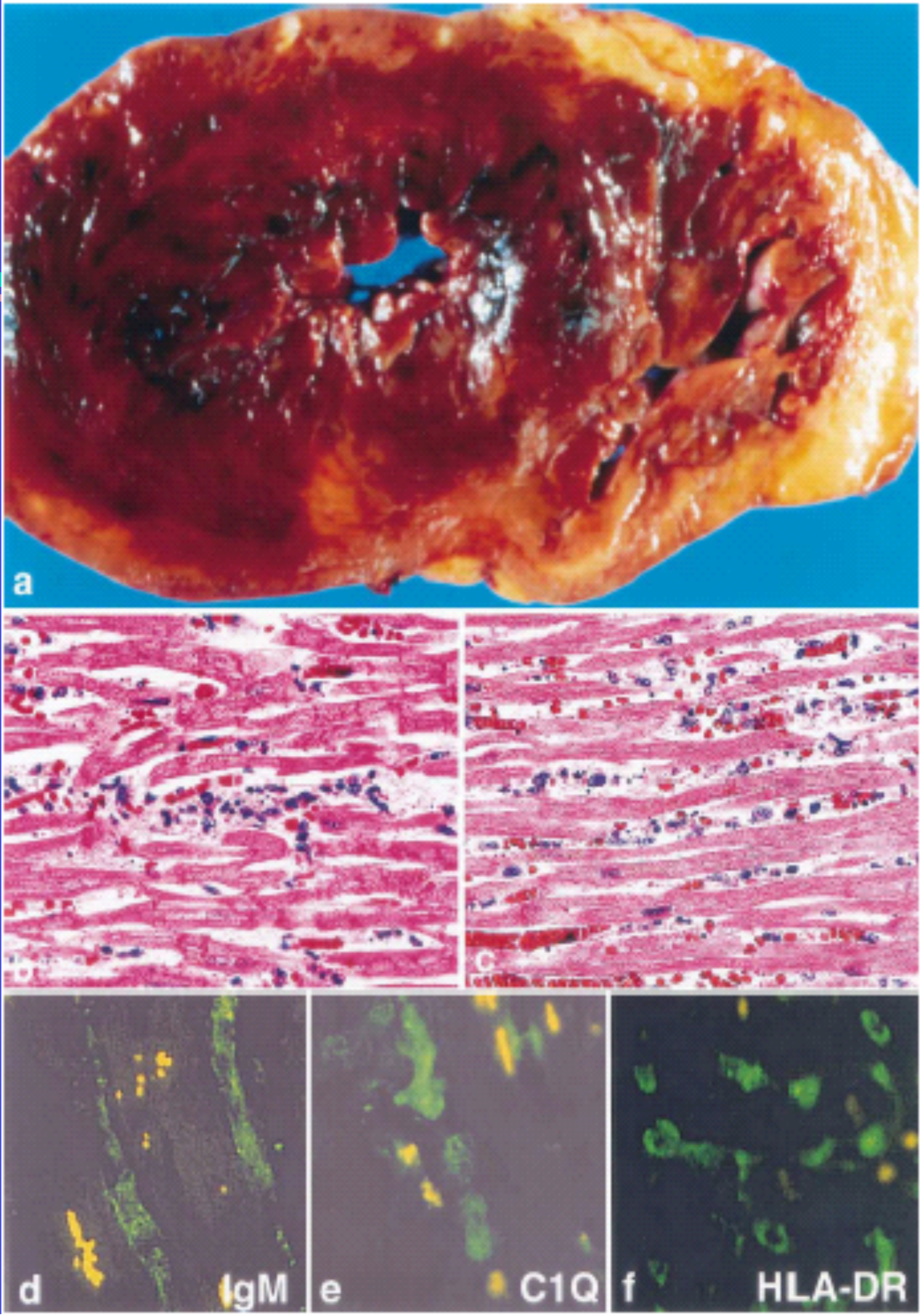
Reference group = Cardiomyopathy, no devices

N = 3,516

Pathology of Rejection

- Hyperacute (antibody-mediated)
- Antibody-mediated rejection (humoral)
- Acute
  - cellular
- Chronic (OB, CAV, CAN, vanishing bile)

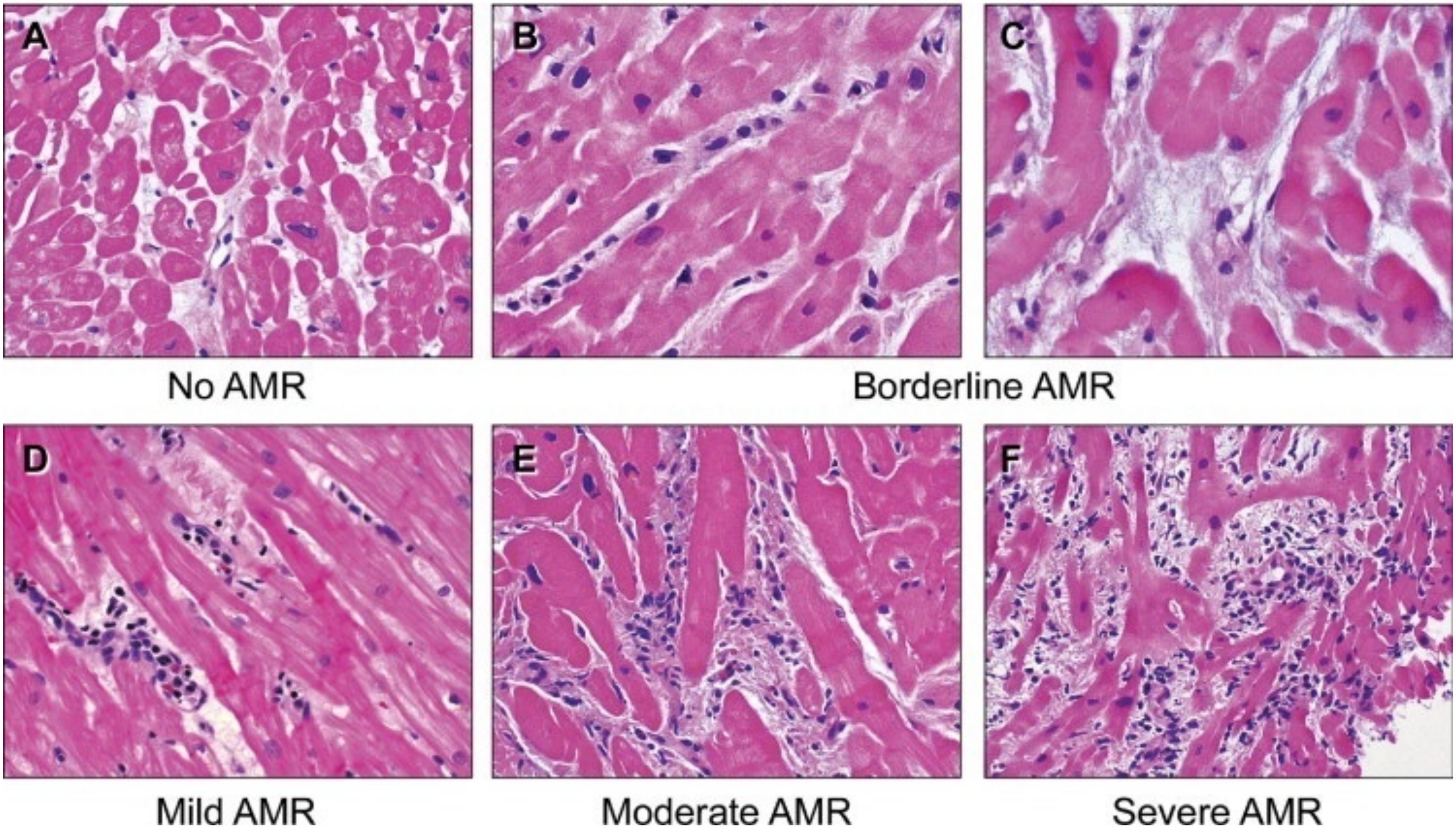
Heart transplant patient who died of humoral rejection. Macros show diffuse hemorrhage in both ventricles. Micros show intravascular macs and neutrophils. IF show capillary positivity for IgM, C1q and HLA-DR.



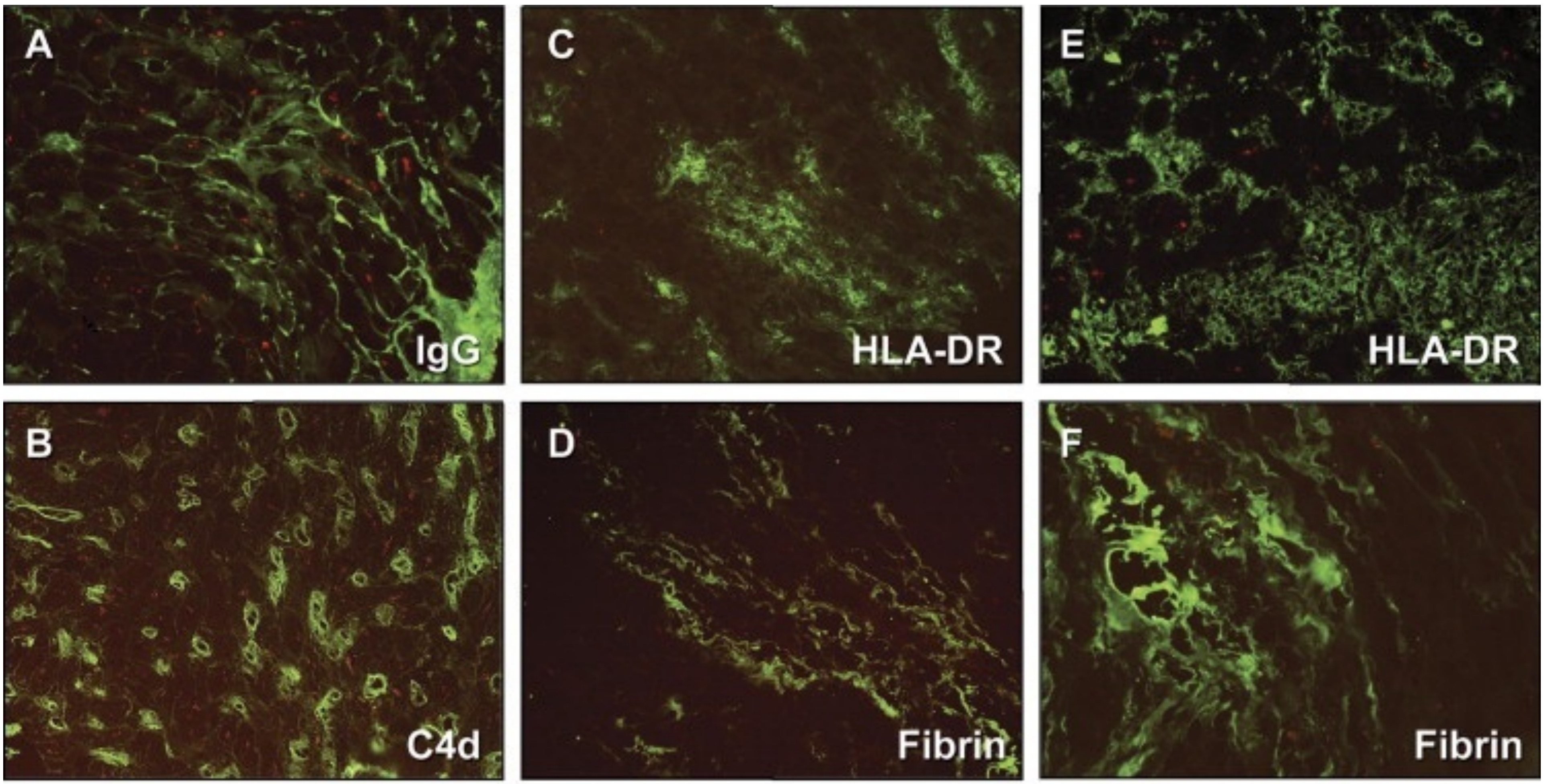
Hyperacute rejection

- < 1% incidence (role of cross-match)
- Minutes to days onset
- Abrupt organ dysfunction
- Preformed circulating Abs
  - complement activation
  - neutophil recruitment
  - platelet aggregation
- Vascular thrombosis

AMR: Histology



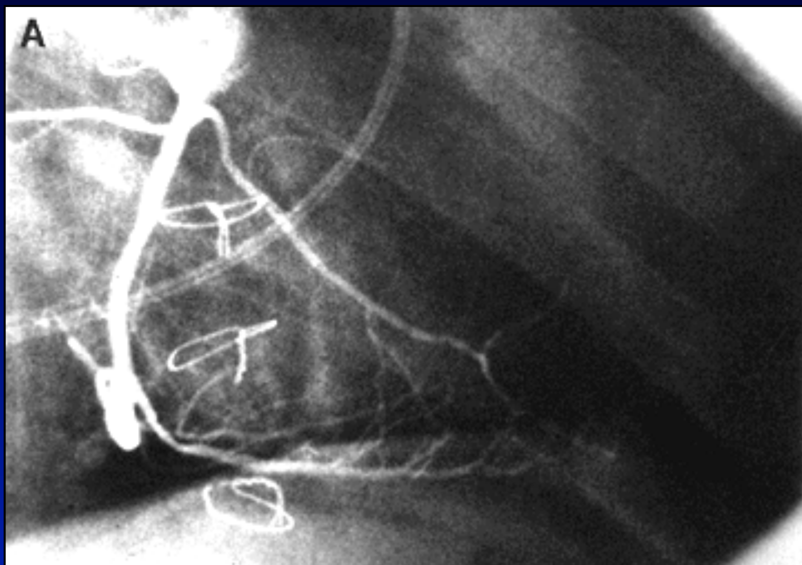
AMR: Immunopathology



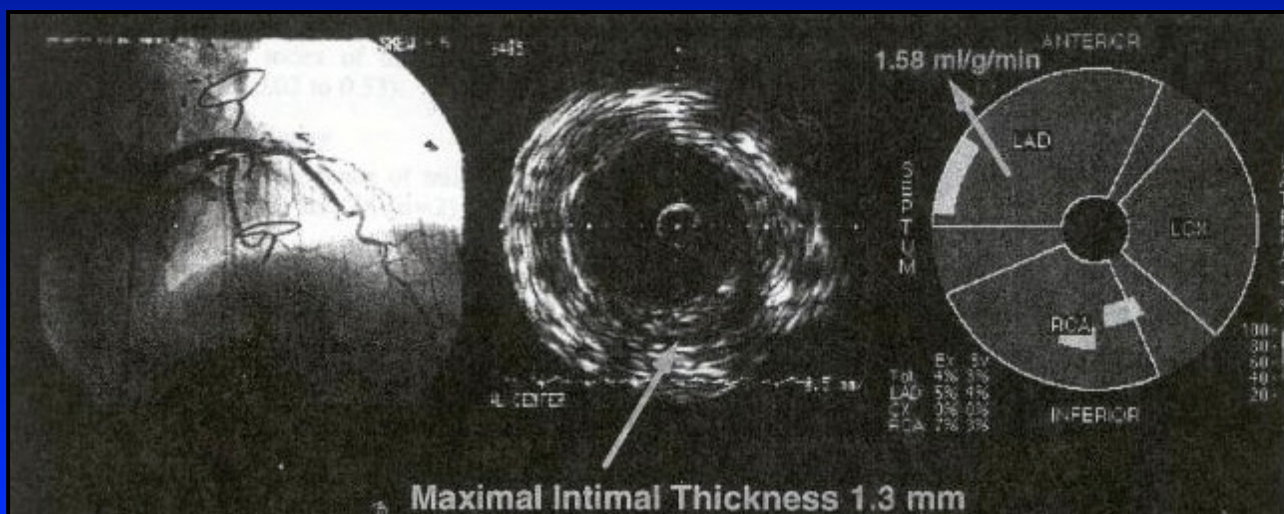
Mild AMR | Moderate AMR | Severe AMR

The Spectrum of Antibody-mediated rejection

Cardiac Allograft Vasculopathy (CAV)



Histology: Chronic AMR?



Management of Antibody-mediated Rejection

"To fight the enemy, first know the enemy"

- **Removal of circulating anti-HLA antibodies**
  - **Plasmapheresis, immune apheresis (adsorption)**
- **Reduction in production/inhibition of anti-HLA antibodies**
  - **Intravenous immune globulin (IVIG)**
  - **B-cell (anti-CD20 monoclonal antibody rituximab); plasma cell (proteasome inhib. bortezomib) depletion**
  - **Cytolytic therapy, tacrolimus/MMF, cyclophosphamide, TLI?, photopheresis?**
- **Anti-complement therapy**
  - **(eculizumab, anti-C5 monoclonal antibody)**
- **High dose steroids, circulatory support, anticoagulation**

Chronic "rejection" (injury)

- Achilles heel (biologic constraint) of solid organ allotransplantation
- Months to years onset
- Insidious decline in organ function
- Chronic healing and scarring
- Vascular (or airway or biliary) dense fibrosis (ischemia)
- Rx-reTx (poor response to conventional immunotherapy

SPECIAL REPORT

HEALTH & TECHNOLOGY: WHAT THE FUTURE MEANS FOR YOU

The Next Frontiers

Newsweek

June 25, 2001

newsweek.msnbc.com

How Technology Will Heal Your HEART

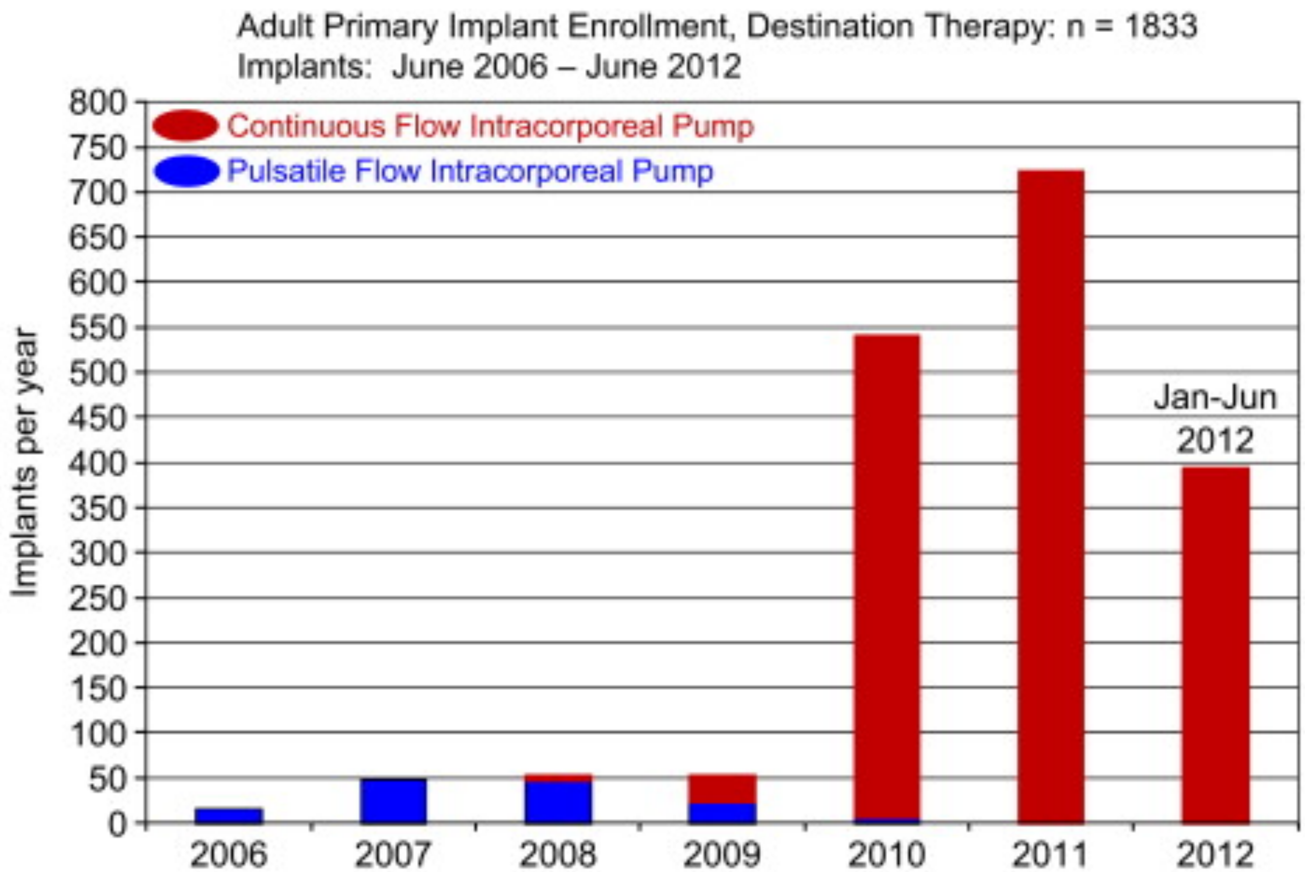
Patient Power on The Web

Made-to-Order Medicine

Robotic Surgery

The AbioCor implantable replacement heart

LVADs

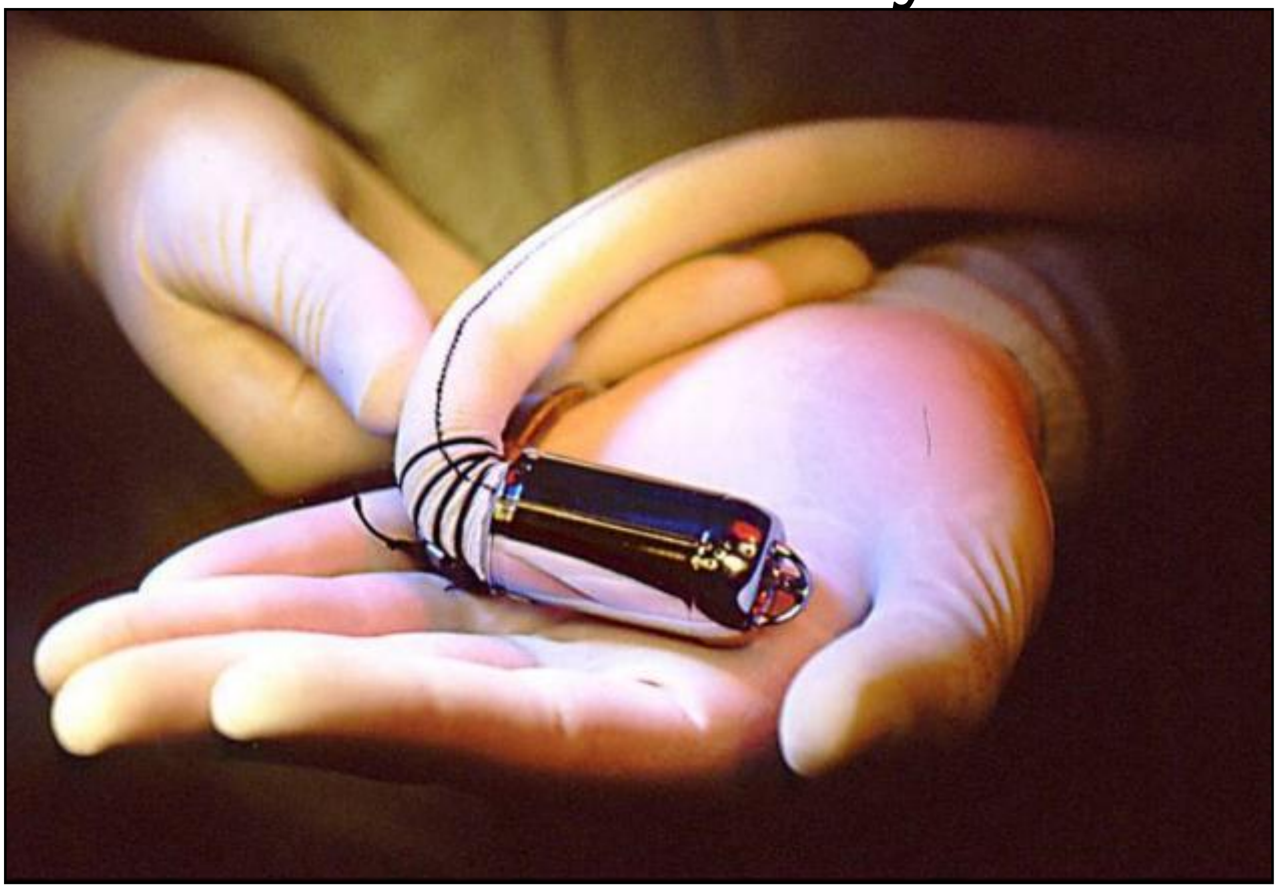


	2006	2007	2008	2009	2010	2011	2012
Cont Intra Pump	0	0	7	32	537	723	395
Puls Intra Pump	15	48	46	22	5	1	0

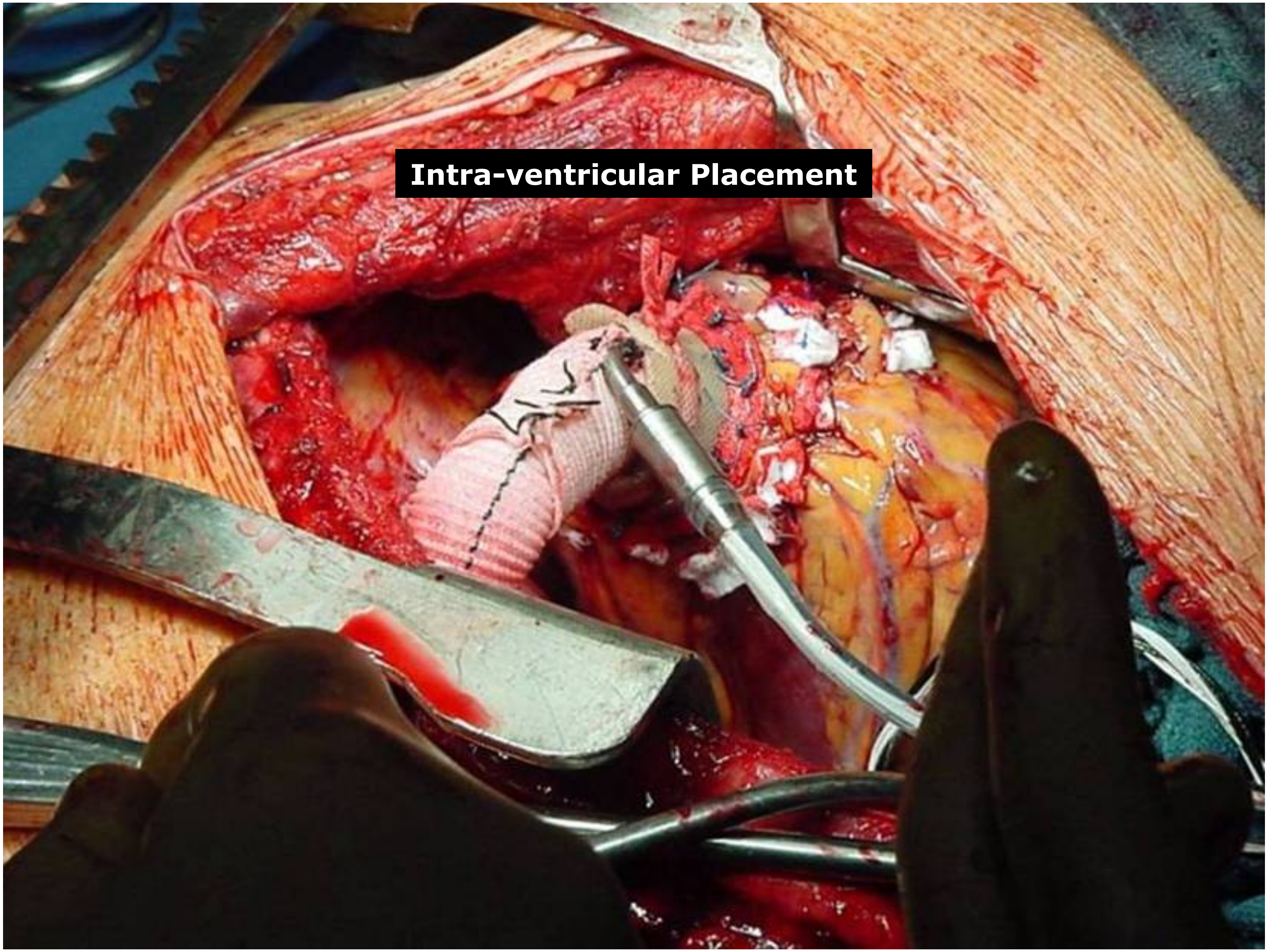
Advantages of Long-Term Mechanical Support

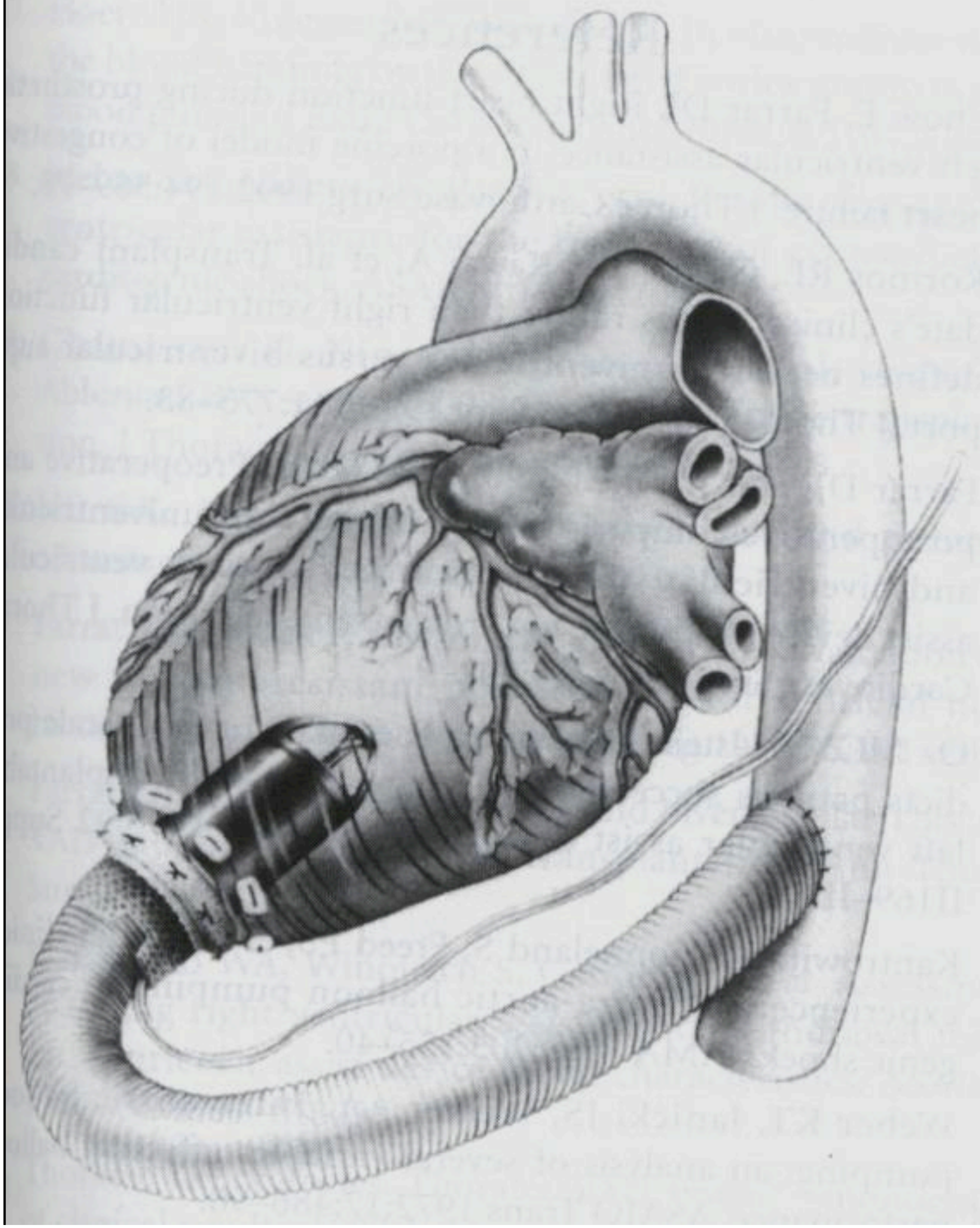
- nutritional status
- muscle mass and tone
- functional capabilities
- end-organ function
- better transplant candidates

Initial clinical experience with the Jarvik 2000 implantable axial-flow left ventricular assist system



Frazier et al.: Circulation. 2002;105:2855-2860


Intra-ventricular Placement



Original Contributions

JAMA®
THE JOURNAL of the American Medical Association
Dec 20, 1985 Vol 254, No. 23

Baboon-to-Human Cardiac Xenotransplantation in a Neonate

Leonard L. Bailey, MD; Sandra L. Nehlsen-Cannarella, PhD; Waldo Concepcion, MD; Weldon B. Jolley, PhD

This report details the first case of cardiac xenotransplantation In a neonate. The recipient, a victim of hypoplastic left heart syndrome (HLHS), survived 20 days. Autopsy findings are documented. The cardiac graft showed only traces of cell-mediated rejection. Graft failure appears to have resulted from a progressive, potentially avoidable humoral response, unmodified by immunosuppression. Cardiac allotransplantation and selective baboon-to-human xenotransplantatlon deserve further exploration as investigational therapy for neonatal HLHS.

(JAMA 1985;254:3321-3329)

Animal and Human Models

We received him from a lab in U.S.

Xenotransplantation

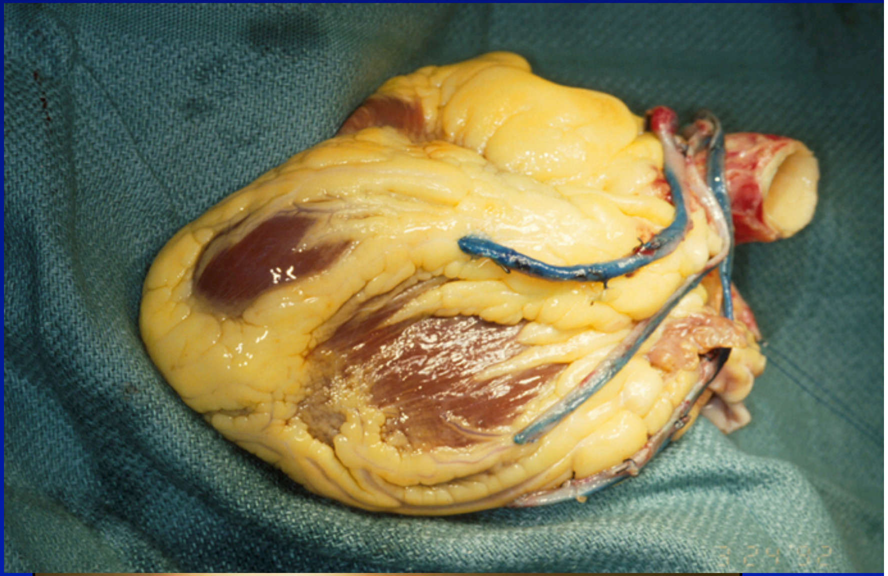
Galactose –alpha-1,3-galactose – main target for human preformed antibodies

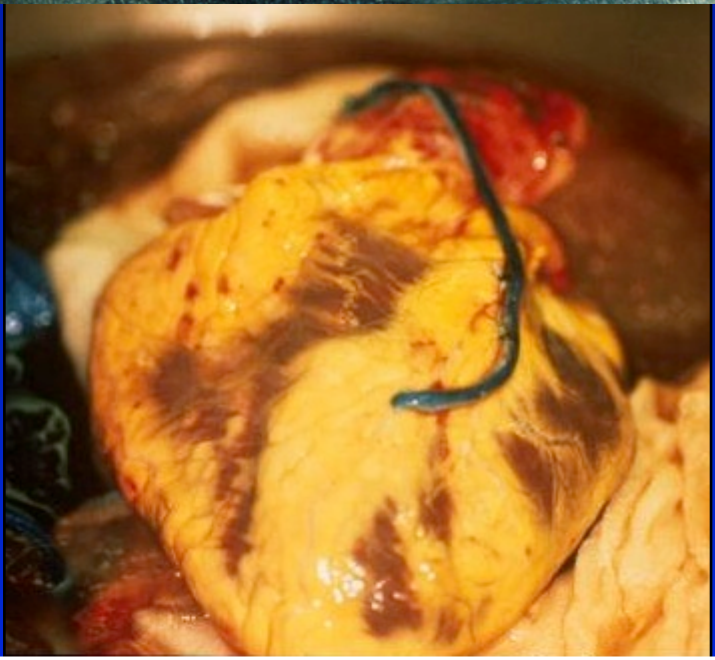
1) With GRKO/HCD55 pigs to nonhuman primates (cardiac xenografts) have a median survival of 90 days

2) Further genetic modifications of pigs ongoing by introduction of human anticoagulant or antithrombotic protein-encoding genes (thrombomodulin, tissue factor pathway inhibitor) as well anti-inflammatory and anticoagulation genes will be needed for viable long-term outcome and organ function

3) Biosafety issues related to transmission porcine endogenous retroviruses (PERV)

Coronary Artery Disease





Organ Donor Management

International clinical trials of heart and lung organ management prior to implantation:

PROCEED II
NOVEL
INSPIRE

Old and the New

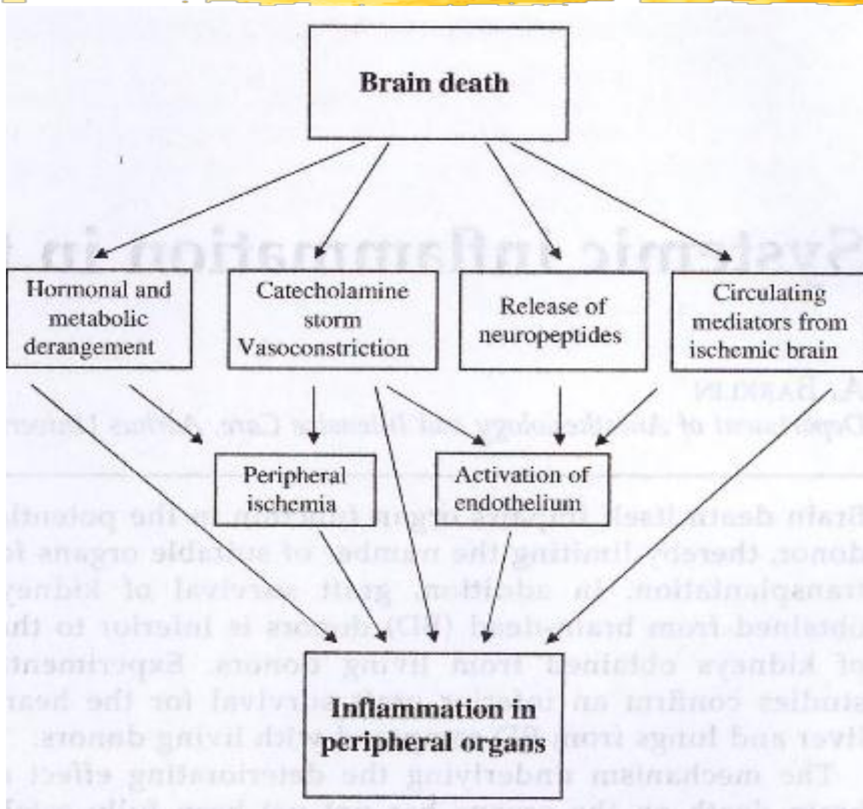
1) Marginal donors (*e.g.*, HIV+, HCV+, older, longer ischemic time, CAD, valvular disease, LVH)

2) Organ Care System *(Transmedic)* [Hearts and Lungs + pumping kidneys]

3) Cell therapy (*e.g.*,stem cells, pluripotent cells, BMC)

4) Growth and generation of whole organs on various scaffolds

Donor – brain death



Leads to inflammatory response – in heart

- Increase levels of IL-6, IL-6 receptors, P-selectin, VCAM-1, TNF-a
- Higher levels in failing vs, non-failing hearts
- TNF-a elevation predicted poor outcome

Conclusions

- **The first 60 years of organ transplantation has witnessed tremendous progress in management of acute rejection and one year graft survival approaches 90% for most organs.**

- **Attention is now refocused on improving long-term outcomes with attention focused on combating antibody and innate mediated injury, reducing renal and cardiovascular morbidities, donor organ management prior to implantation, and personalized immunosuppression**